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## **Women's health and wellbeing: the roles of early life adversity, stress and lifestyle**

van Dammen, Lotte

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# Chapter

# 10

Summary of the findings  
and general discussion



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In this thesis we investigated the association between early life adversity and poor cardiometabolic health in adulthood, and potential underlying neuroendocrine, behavioral and psychological pathways. The effectiveness of lifestyle interventions to improve cardiometabolic health and mental wellbeing among obese women of reproductive age was assessed, as well as the role of a history of childhood adversity in the effectiveness of a lifestyle intervention in improving body composition.

### **10.1.** *Childhood adversity and cardiometabolic health in adulthood (Chapter 2)*

Cross-sectional analyses were carried out among 115 women of reproductive age to assess if childhood adversity is associated with poor cardiometabolic health in adulthood. Although we did not find associations between childhood adversity and poor cardiometabolic health in adulthood, childhood adversity was associated with poorer self-reported sleep quality, more external eating behavior and increased stress symptoms in adulthood. These unhealthy behaviors and symptoms may lead to future impaired cardiometabolic health, warranting further follow-up of this group in order to assess long-term effects on cardiometabolic health.

### **10.2.** *Early life adversity and HPA-axis and ANS reactivity (Chapter 3)*

In a systematic review of the literature regarding the associations between maternal depression during pregnancy and offspring HPA-axis and ANS reactivity, a total of 13 studies with 2271 mother-infant dyads were included. Meta-analysis was not possible because of the large differences between studies in terms of methods to assess maternal depression and stress reactivity in the offspring. Three studies described an independent association between maternal depression during pregnancy and increased ANS reactivity and altered cortisol stress reactivity in the offspring, whereas the other 10 studies did not find such an association. Prenatal exposure to depressive symptoms as an independent factor does not seem to be consistently associated with HPA-axis or ANS stress reactivity in children, but high heterogeneity among studies preclude robust conclusions.

### **10.3.** *Childhood adversity and cortisol and DHEA (Chapter 4)*

Childhood adversity may increase the risk of impaired mental health in later life differently for boys and girls, and altered HPA-axis functioning may be an important mechanism in this association. In this cross-sectional study among 190 adolescents, the association between person- and environment related childhood adversity and cortisol and DHEA levels in adolescence was assessed. There appeared to be sex-specific associations between person-related childhood adversity and increased levels of DHEA among girls, and no associations between environment-related childhood adversity and cortisol or DHEA levels in girls. Person-related childhood adversity was associated with higher cortisol levels in boys, and environment-related childhood adversity was associated with increased levels of cortisol and DHEA among boys. These results indicate that different types of childhood adverse events may result in altered HPA-axis functioning in a sex-specific way, with possible future consequences for mental health.

### **10.4.** *Effects of preconception lifestyle intervention on cardiometabolic health and QoL (Chapter 5)*

The effects of a six month preconception lifestyle intervention on cardiometabolic health and quality of life were assessed in a RCT carried out among 577 obese infertile women. The lifestyle intervention led to a reduction of -3.1 kg (95% CI:-4.0 to -2.2 kg) in weight and improved BMI, waist- and hip circumference, blood pressure, insulin, glucose, HOMA-IR and higher physical QoL during and directly after the six month intervention. There were no effects on mental QoL. The composite outcome metabolic syndrome was less prevalent after the six month lifestyle intervention. This suggests that a preconception lifestyle intervention in obese infertile women leads to improved cardiometabolic health outcomes and physical QoL.

### **10.5.** *Effects of preconception lifestyle intervention on cardiometabolic health six years post randomization (Chapter 6)*

In order to assess the long-term effect of preconception lifestyle intervention, cardiometabolic health was assessed in two RCT's among 150 infertile women who participated in the six year follow-up. The lifestyle interventions did not lead to improved cardiometabolic health six years after randomization, although women who were successful in losing 5-10% bodyweight or reached a BMI <29 kg/m<sup>2</sup> during

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the six month intervention period, did show improved cardiometabolic health outcomes. This indicates that short-term successful change in lifestyle is important for long-term cardiometabolic outcomes.

**10.6.** *Effects of preconception lifestyle intervention on mental well-being (Chapter 7)*

In order to assess the effects of a preconception lifestyle intervention on levels of perceived stress, mood symptoms, sleep and QoL, women who participated in a lifestyle intervention RCT carried out among 577 obese infertile women, were followed. A total of 178 women received a questionnaire packet five years after randomization, and filled out additional questionnaires in the six year follow-up. The lifestyle intervention did not lead to improved levels of perceived stress, mood symptoms, sleep quality and QoL five to six years post randomization. Selective participation resulted in a subgroup of women who participated in the follow-up, primarily those with higher baseline mental QoL, and women who did not benefit from the intervention in terms of improved physical QoL within one year post randomization, which may have resulted in an underestimation of the intervention effect. In order to reduce selective participation in future research, novel strategies are needed to include intervention participants in follow-up studies.

**10.7.** *Effects of lifestyle intervention on symptoms of depression and anxiety (Chapter 8)*

In a systematic review and meta-analysis, the effects of lifestyle interventions among overweight and obese women of reproductive age on symptoms of depression and anxiety were assessed. A total of five studies, with 571 women included in the meta-analysis, showed that the lifestyle interventions consistently reduced symptoms of depression and anxiety among overweight and obese women of reproductive age. This suggests lifestyle interventions among overweight and obese women of reproductive age are effective in improving mental wellbeing, which might result in improved long-term health. Future research should include measures of depression and anxiety as an outcome after a lifestyle intervention, in order to assess potential mechanisms of lifestyle interventions on reduced symptoms of depression and anxiety among a large amount of studies.

### 10.8. *Childhood adversity and lifestyle intervention effectiveness (Chapter 9)*

In this chapter, we assessed whether the effects of a lifestyle intervention in obese infertile women on cardiometabolic risk depended on women's exposure to childhood adversity. The effect of a lifestyle intervention among obese women on cardiometabolic health was examined in a RCT including 577 women, of whom 110 participated in the six year follow-up. The lifestyle intervention reduced weight by 10 kg (95% CI -18.5 to -1.5) among women who were exposed to childhood adversity, whereas no effects on weight loss were observed for those who were not exposed to childhood adversity. Similar effects were observed for BMI, waist- and hip circumference and body fat percentage. This suggests that women who experienced childhood adversity may be more receptive for lifestyle advice, leading to improved body composition after a lifestyle intervention.

## General discussion

### 10.9. *Pathways from early life adversity to poor cardiometabolic health*

Previous research suggests that early life adversity may lead to altered HPA-axis functioning, more unhealthy behavior, increased stress and mood symptoms, negative personality traits and impaired cardiometabolic health throughout development into adulthood (1-7). This thesis adds to the existing literature by providing evidence that early life adversity may alter stress reactivity to some extent (Chapter 3), that person- and environment related childhood adverse events have sex-specific effects on increased cortisol and DHEA levels in girls and boys, respectively (Chapter 4), and that childhood adversity may not lead to poor cardiometabolic health in women of reproductive age yet, although childhood adversity did lead to impaired sleep, poor eating behavior and more stress symptoms (Chapter 2). Altered stress reactivity, HPA-axis functioning, impaired sleep, poor eating behavior and stress symptoms have all been linked to poor cardiometabolic health in adulthood (8-13). The observed associations between childhood adversity and altered HPA-axis functioning, poor health behaviors and stress symptoms could have future implications for cardiometabolic health, and further follow-up could give insight in future cardiometabolic risk. Interventions may be important

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to reduce the cardiometabolic risks and may target altered HPA-axis functioning, poor sleep quality, eating behavior and stress symptoms. Psychosocial interventions have been suggested in children to improve cortisol regulation (14), mind-body interventions, in which the mind's capacity to affect the body and the physiological responses is utilized, have been shown to improve sleep quality in adulthood (15), and reduce characteristics of distressed personalities in adulthood (16). These interventions might also improve future cardiovascular health, although evidence is currently lacking and more research is necessary to confirm this.

#### **10.10. *Timing and motivation in lifestyle interventions***

The LIFEstyle study provided unique evidence on the effects of a preconception lifestyle intervention in obese infertile women on cardiometabolic health and mental wellbeing. Previous research suggested that lifestyle interventions have limited positive effects on weight loss and cardiometabolic health (17). Within six months post randomization, our intervention showed promising results regarding weight loss (approximately 3 kg), improved cardiometabolic health and physical QoL (Chapter 5). These positive effects could have been the results of the increased motivation of the intervention participants to lose weight, in order to increase their pregnancy chances. However, five to six years post randomization, we were unable to show sustained positive effects on weight, cardiometabolic health and mental wellbeing, although selective participation reduced statistical power and led to bias (Chapter 6 & 7). Another study showed that an eight-year lifestyle intervention among patients with type 2 diabetes was effective in reducing bodyweight and improving mental wellbeing (18, 19). Mean weight loss was approximately 8 kg one year after the start of intervention, and 5 kg eight years after the start of the intervention. Almost 5000 patients participated in this latter intervention, with high follow-up rates at eight years and no selective participation. In the LIFEstyle study, follow-up rates five to six years after randomization did not exceed 30% of the original 577 randomized women. In our study, there were indications for selective participation, such that those women with higher baseline mental wellbeing participated in the follow-up, as well as the women who benefitted less from the intervention in terms of improved physical QoL within the first year post randomization. Selective participation reduces the reliability of the null results found five to six years post randomization, regarding weight loss, cardiometabolic health and mental wellbeing, making it difficult to draw conclusions. Selective participation may have led to an underestimation of the

observed effects, since women who benefitted most from the intervention in terms of improved quality of life within the first year, did not participate in the follow-up.

Lifestyle interventions during pregnancy have been studied previously, and the main aims of these interventions were to reduce risk of gestational diabetes mellitus (GDM), limit gestational weight gain and improve the intra-uterine environment (20). Lifestyle interventions during pregnancy have been shown to reduce the risk of GDM (20, 21). In the RADIEL trial a lifestyle intervention of approximately five months duration, during pregnancy, reduced post-partum impairment of glucose regulation of the women (22). The UPBEAT trial consisted of an eight-week behavioral intervention during pregnancy and showed no positive effects on GDM risk (23). In the LIMIT trial pregnant women received a lifestyle intervention starting at the end of the first pregnancy trimester until 36 weeks of gestation, which did not result in lower risk of GDM nor improved maternal health in general (24). The effects of lifestyle interventions in the preconception period and interventions during pregnancy on weight loss cannot be compared, since interventions during pregnancy aim at reducing gestational weight gain, whereas preconception interventions aim at weight loss.

During the design of the LIFEstyle study it was hypothesized that women may want to improve their lifestyle during the preconception period, in order to increase their chance of pregnancy. Women allocated to the control group could start fertility treatment promptly as indicated, whereas women allocated to the intervention group received a lifestyle intervention followed by fertility treatment as indicated. This study design may have a limitation, such that women in the intervention group may have perceived their fertility treatment as delayed, compared to the control group. Ideally, the design of the study would have included a “waiting-list” period of six months in the control group before women received infertility treatment, putatively resulting in low inclusion rates and also raising ethical questions regarding withholding treatment. The women included in the LIFEstyle study were infertile, such that these women tried to conceive for at least one year before inclusion or had chronic anovulation. Previous research suggests infertility has major impact on mental wellbeing and is associated with anxiety (25). The women who participated in the LIFEstyle study might have been anxious they would not conceive, consequently reducing motivation to lose weight. Lifestyle interventions in overweight or obese women of reproductive age who are anticipating pregnancy, and are not yet trying to conceive, might be more effective if women are more motivated to first improve lifestyle before trying to conceive. Effective lifestyle interventions in women of reproductive age not trying to conceive



yet, may not only improve women's health, but could also improve the intrauterine environment during a subsequent pregnancy (26). Further research will have to provide insight in the effects of the lifestyle intervention on offspring's health.

### 10.11. *Mental and physical wellbeing*

The last couple of decades attention to the link between mind and body has increased in medicine, shifting from primarily disease-centered care to “whole person” care, including mental wellbeing (27). Our understanding of mind-body interaction is still expanding (28), and results presented in this thesis further contribute to this expanding knowledge (Figure 1).

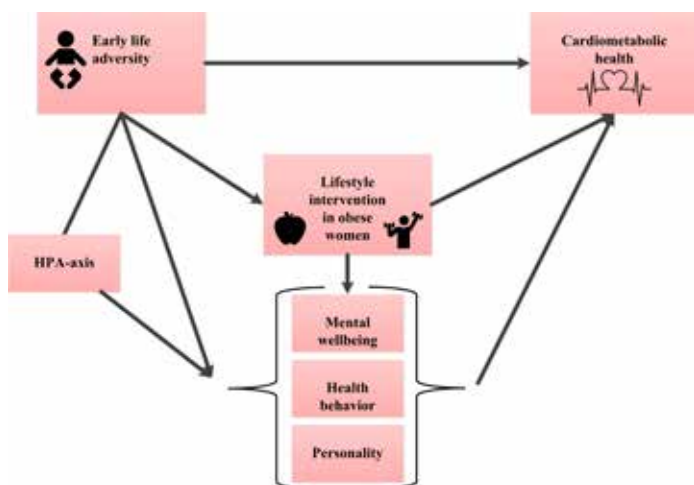


Figure 1. Model presenting the main topics and pathways described in this thesis (Chapter 1).

Findings presented in Chapter 2, 3 and 4 demonstrated that early life adversity is associated with altered bodily stress responses to some extent in childhood, altered HPA-axis functioning in adolescence, and with poor health behaviors and stress symptoms in adulthood. These findings indicate mind-body interactions already occur during childhood and may have long-term negative consequences for cardiometabolic health. The period from conception to adolescence may be seen as a sensitive period, and adverse experiences or environments during this period can have detrimental effects on development and adult health.

It has been shown that obesity impairs mental wellbeing (29), and we have now provided evidence that lifestyle improvement leads to better mental wellbeing (Chapter 8). Lifestyle improvement may lead to better mental wellbeing through

various mechanisms. Weight loss itself may lead to improved HPA-axis functioning (30), with positive effects on depressive symptoms (31). Different dietary factors could also play a role, such as decreased sugar intake and increased omega-3 fatty acids intake, since these dietary factors are related to improved mental wellbeing (32). Increased physical activity has also shown to improve mental wellbeing (33), possibly through lower  $\beta$ -endorphin plasma levels (34). Previous research suggests mental wellbeing as an important outcome for individuals themselves, since this is an important factor in daily life functioning (35). In the process of literature screening for the systematic review and meta-analysis (Chapter 8) it became clear that a large proportion of the studies could not be included because symptoms of depression or anxiety were not assessed as outcomes after a lifestyle intervention. Given the vicious cycle of obesity, impaired mental wellbeing and subsequent weight gain, it is important to assess the effects of lifestyle interventions on mental wellbeing in future studies. However, although the meta-analysis in Chapter 8 provided evidence of improved mental wellbeing after lifestyle intervention, the LIFeStyle study intervention did not lead to improved mental QoL within one year post randomization (Chapter 5). The lack of effect on mental QoL may be partially explained by the primary motivation of the women participating in this trial, which was to become pregnant. Ongoing infertility may have overshadowed the potential positive effect of the intervention on mental QoL. Additionally, the LIFeStyle study intervention did not lead to improved mental wellbeing five to six years post randomization, although selective participation may have led to an underestimation of the results (Chapter 7). Based on the current results, future studies may consider including mental wellbeing as a lifestyle intervention outcome in order to further determine the effects of lifestyle interventions on mental wellbeing in different populations.

### 10.12. *The obesity pandemic*

An unfavorable early life environment, unhealthy diet and physical inactivity contribute to the current obesity pandemic and consequent cardiovascular disease in adulthood (36-38). Preconception lifestyle interventions aiming at a healthy diet and increasing physical activity are effective in improving cardiometabolic health (Chapter 5). In order to prevent the development of obesity in offspring, interventions to improve the early life environment from preconception onwards, could play an important role. Interventions aiming at the prevention of early life adversity, obesity and improving health may be more effective if the interventions not only target the individual, but even more so the environment and community the individual is

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part of. Community capacity, described as empowerment of communities to take on responsibility for building healthy environments, was found to be effective in reducing childhood adversity (39). Community networks create collaborations among local multidisciplinary service providers and restructure natural supports and resources in order to meet the local community's needs, taking local culture into account. These community interventions may also lead to significant costs savings in health care and social services (39).

The preconception period may not only be important to improve women's health, but could also be a window of opportunity to improve the early environment, both during pregnancy and after birth, for the offspring, and to provide advice to the future parents in order to reduce childhood adversity rates. Investing in early development and improving the environment could also have important positive economic consequences (Figure 2) (40). Early investment generates return on investment on an individual level in terms of higher education, greater earnings and improved physical and mental wellbeing. On a societal level, early investment may reduce crime rates, and could lead to public expenditure savings and increased tax revenues (40, 41). Previous research suggests the right nutrition and environment during the first 1000 day window between pregnancy and 24 months of age has important effects on children's growth, development and lifelong health (42). At the launch of the 1000 days foundation (<https://thousanddays.org/>), Hillary Clinton stepped forward as a firm advocate of this initiative. Besides the importance of the right nutrition during the first 1000 days, childhood adversity is another important factor to consider during this critical developmental period. In the Netherlands, an intervention aiming at the prevention of child abuse and neglect during the first 1000 days, proved to be successful in reducing interpersonal partner violence victimization and child abuse (43, 44). The intervention consisted of nurse home visits in disadvantaged women and was based on the Nurse-Family Partnership (NFP) intervention developed by David Olds et al., and has previously shown to be effective in the United States in reducing child abuse (45). Furthermore, the intervention showed positive effects on maternal life course outcomes and reduced child abuse and neglect up to 15 years after the birth of the child (46).

**Figure 2.** Rate of return to investment in human capital, adapted from Heckman, 2008 (41).



### 10.13. *Childhood adversity and lifestyle interventions*

In Chapter 9 the effectiveness of a lifestyle intervention was described for those with and without childhood adversity. The intervention improved body composition among women who were exposed to childhood adversity, possibly because these women were more receptive to lifestyle advice. A large body of literature describes determinants of successful lifestyle change, including high motivation and high socioeconomic status (47, 48). This thesis adds that childhood adversity may also be an important factor to consider in lifestyle intervention effectiveness research. The lifestyle intervention led to 10 kg weight loss six years after the intervention among those who experienced childhood adversity (Chapter 9), which is three times higher than the weight loss among the entire intervention group six months after the intervention (Chapter 5). Although these findings need to be confirmed in future research, the current results suggest childhood adversity is an important factor to consider in lifestyle interventions, and the magnitude of the effect may be greater than previously established determinants of successful weight loss (47, 49, 50). Clinicians and researchers involved in the development of new interventions aiming at behavior change, should consider screening participants before inclusion on childhood adversity history. Interventions may need to be tailored to participants who were exposed to childhood adversity, and those who were not exposed, such that the latter group might benefit more from other types of interventions.

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## Conclusion

Early life adversity is associated with poor health behaviors and more stress symptoms, possibly through altered HPA-axis functioning, and those factors may lead to future poor cardiometabolic health. A preconception lifestyle intervention was successful in improving cardiometabolic health, and a meta-analysis showed that among overweight and obese women of reproductive age lifestyle interventions improve mental wellbeing. Childhood adversity seems to be an important factor in effectiveness of lifestyle intervention, and future research should incorporate childhood adversity assessment in lifestyle interventions in order to optimize intervention effectiveness, improve weight loss and potentially reduce costs.

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